REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1-13 are in this case. Claims 1-13 have been rejected under 35 U.S.C. § 112, second paragraph and further under 35 U.S.C. § 103(a). Independent claim 1 has been amended. The claims before the Examiner are directed toward an optical method for testing sensitivity of cells.

§ 112, Second Paragraph Rejections

The Examiner has rejected claims 1-13 under § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Specifically, the Examiner has asserted that step (b) of claim 1 is ambiguous in reciting "exposing a portion of the cells to a drug" because the term "a portion " is a relative term. The Applicant respectfully, but vigorously, disagrees with the Examiner. Figure 1 clearly shows that the drug to be screened according to the claimed method is added to a subset of a population of cells, for example cells obtained from a biopsy. In the absence of a definition, "a portion of the cells" must be construed more than one cell and as many as all the cells. Claim 1, as the independent claim, is purposely written to be broad enough to include all embodiments of the invention. Because, the cells may be cultured before "exposing a portion of the cells to a drug", description in terms of the original number of cells lose relevance. For example, if a biopsy containing one million cells is cultured until 14 million cells are present and one hundred thousand cells are exposed to the drug, does that

represent 10% or 0.7% of the cells? Further, because the cells are assayed individually, the absolute number required for an assay is a function of the magnitude of the "measurable degree of fluorescence" which is in turn a function of the "assay device" of claim 1; clause (e). Thus, the independent claim would be unduly limited in scope by recitation of a specific number of cells.

Further specifically, the Examiner has asserted that "capable of" and "can be" of step (c) of claim 1 fails to recite a positive limitation. The Applicant does not find in claim1 clause (c) "can be". The Examiner has further rejected clause (c) of claim 1 for reciting "substance... imparting a measurable degree of fluorescence", erroneously asserting that the phrase implies a fluorescent substance. The Applicant respectfully points out that the ellipsis replaces the phrase "capable of". Thus, the Examiner takes exception to the phrase "substance capable of imparting a measurable degree of fluorescence" for two reasons, because it does not recite a positive limitation and because it does not specify a "fluorescent substance". The Applicant replies to these two points together since they refer to a single phrase.

Firstly, "substance capable of imparting a measurable degree of fluorescence" is a positive limitation. Secondly, that limitation is far broader than a limitation imposed by the phrase "fluorescent substance". Enabling description of material included under this phrase is found in the specification on page 7; lines 15-20:

> According to method **10** (FIG. **1**) cells are incubated with the substance capable of imparting a measurable degree of fluorescence. The substance capable of imparting a measurable degree of fluorescence may be, for example, a substance that differentially stains mitochondria of living cells, a precursor of a fluorescent substance that differentially stains living cells or a fluorophore that stains nucleic acids. (emphasis added)

Thus, the phrase in question refers to at least two categories of substances which are not fluorescent substances *per se*, although fluorescent substances *per se* are

included within the positive limit imposed by the phrase in question. These three categories are claimed in claim 9. The specification further provides an example of "a substance that differentially stains mitochondria of living cells" (Rh123) on page 10; lines 16-28. The specification further provides an example of "a fluorophore that stains nucleic acids" (AO; page 10; line 29 to page 11; line 6). AO, for example, gives green fluorescence when bound to DNA and red fluorescence when bound to RNA. Thus, AO is further an example of "a precursor of a fluorescent substance... "

The Applicant advances the same argument in traversing the Examiner's rejection of similar phrasing in claims 8 and 9.

The Examiner has further taken exception to clause (d) of claim 1 as being ambiguous in reciting "causing the cells to reside" in "defined locations". The Applicant respectfully points out that the claims may rely upon the specification to provide enablement. In this case, enablement for the phrase in question is provided in the specification on page 6; line 26 to page 7; line 3. It is to be stressed that the specified enabling description is illustrative, and not limiting. Therefore, the Applicant would necessarily object to introducing enabling portions of the specification into the phrase in question. One ordinarily skilled in the art would be able to accomplish the claimed step in a wide variety of ways, including, but not limited to suction, settling, centrifugation, electrophoresis and micromanipulation.

The Examiner has further taken exception to clause (d) of claim 1 as failing to recite a positive limitation of the claim for using the phase "can be individually accessed". The Applicant responds by amending the offending phrase to read --are individually accessible--.

The Examiner has further taken exception to claim 1 as omitting an essential step of "correlating". The Applicant respectfully calls the attention of the Examiner to clause (e) of claim 1 as currently filed:

(e) assaying by means of said assay device at least a portion of the cells in said defined locations at least one time as a means of determining the drug sensitivity thereof. (emphasis added)

In the underlined phrase, "thereof" refers to cells assayed by said assay device. Thus, assaying is presented as a means of determining the drug sensitivity (of the cells). Because the assay directly indicates the sensitivity, correlating is inherent in the claimed step. However, in order to expedite prosecution, the Applicant amends clause (e) of claim 1 to include the phrase "...and correlating a result of an assay conducted by said assay device to...". The Applicant stresses that this amendment does not constitute an introduction of new matter because it is supported both by claim 1 as originally submitted and by the specification (emphases added):

> (page 12; lines 6-7) "The results can be correlated to drug efficacy,..."
>
> (page 13; lines 15-16) "...to correlate the sensitivity or resistance of the cells to the drugs..."
>
> (page 13; lines 27-30) "A very good correlation was found between the degree of growth inhibition estimated from the number of cells counted, and the decrease in fluorescence intensity as measured for the Rh123 stained cells."

The Examiner has asserted that claim 9 is indefinite in reciting "overlapping Markush groups". The Applicant respectfully expresses confusion over this rejection since claim 9 as currently filed contains a single Markush group which does not overlap any other claimed Markush group. Assuming that the Examiner intended "overlapping terms within a Markush group", the Applicant offers the following explanation to traverse the Examiner's objection. The Markush group of claim 9 contains three terms:

(a) a substance that differentially stains living cells;

(b) a precursor of fluorescent substance that differentially stains living cells; and
(c) a fluorophore that stains nucleic acids.

By definition, the precursor of (b) and the substance of (a) cannot overlap since (a) is derived from (b) by a process (e.g. chemical process or biological process) which changes (a). Thus, logically speaking, (a) is not equal to (b) in every case.

In sharp contrast to terms (a) and (b), the flourophore of term (c) is not defined as an item which "differentially stains living cells". In fact, the flourophore of term (c) would be expected stain nucleic acids (e.g. DNA or RNA) in solution, as well as in cells. Thus, logically speaking, (c) is not equal to (a) or (b) in every case. Further, like (a), (c) cannot be a precursor because it is a substance (see above).

The Examiner's rejection of claim 9 based on overlapping terms of a Markush group is traversed.

The Examiner has asserted that claims 10 and 11 are indefinite in reciting "further including the step of" because it is unclear what step is further included by the claim. The Applicant responds by pointing out that in each of the claims in question, the additional step for further inclusion is clearly indicated by serially lettered clauses (f) and (g) respectively. Further, these additional clauses are not inherently part of the base claims from which claims 10 and 11 depend.

Specifically, claim 10 recites: "...claim 1, further including the step of: (f) reporting results from said assaying." The step of reporting is not present in claim 1, while "said assaying" finds antecedent basis in claim 1. The intransitive verb "reporting" is defined by dictionary.com as "To make a report". The noun "report" is, in turn, defined as "An account presented usually in detail". Thus, the claimed additional step further limits the base claim.

Further specifically, claim 11 recites "...claim 10, further including the step of:

(g) processing said results to give at least one item selected from the group consisting of:...". "Said results" of claim 11 find antecedent basis in claim 10. The claimed step of "processing" is not present in either claim 10 or claim 1 from which. Processing describes a transformation of numerical data to a graphical format, as indicated by the Markush group of claim 11. This claim imposes further limits on the reporting of claim 10.

The Examiner's rejections based upon § 112, Second Paragraph are traversed.

§ 103(a) Rejections

The Examiner has rejected claims 1-4 and 7-13 under §103(a) as being obvious with respect to Anderson et al (U.S. 6,180,343; hereinafter Anderson) in view of Weinreb et al. (U.S. 4,729,949; hereinafter Weinreb) and has rejected claims 5 and 6 as being obvious with respect to Anderson and Weinraub further in view of Condon et al. (U.S. 6,168,944; hereinafter Condon)

Anderson teaches use of labeled peptides (Column 23; lines 16-24):

> "Thus, the methods of the present invention comprise introducing a molecular library of fusion nucleic acids encoding randomized peptides fused to GFP into a plurality of cells, a cellular library. Each of the nucleic acids comprises a different nucleotide sequence encoding GFP with a random peptide. The plurality of cells is then screened, as is more fully outlined below, for a cell exhibiting an altered phenotype. The altered phenotype is due to the presence of a bioactive peptide." (emphasis added)

Thus, Anderson teaches against the present invention by teaching exposure of cells to a single substance which attempts to be both a "drug" (i.e. bioactive peptide) and a "substance capable of imparting a measurable degree of fluorescence" (i.e. GFP portion of fusion protein). The Applicant has therefore responded by amending claim 1 to include the limitation:

"...wherein the drug and said substance capable of imparting a measurable degree of fluorescence are separately applied." in order to eliminate potential confusion concerning this important difference. Support for this amendment is found

in Examples 1 and 2 (pages 12 -15) of the specification as currently on file. The Applicant stresses that this amendment does not constitute an introduction of new matter.

Separate application of "a drug" and a "substance capable of imparting a measurable degree of fluorescence" offers significant advantage with respect to the teachings of Anderson. For example, it permits assay of non-peptide drugs. Further, it allows parallel assay of drug/substance pairs in different cellular backgrounds without the need for cell transformation. Further, a bioactive peptide may exhibit altered activity when administered as a GFP fusion protein according to the teachings of Anderson.

In summary, because Anderson teaches against the present invention, it would have been infeasible for one ordinarily skilled in the art to arrive at the present invention using the teachings of Anderson as a basis for development. The Examiner's rejections based upon § 103(a) relying upon the teachings of Anderson are traversed.

In view of the above amendments and remarks it is respectfully submitted that independent claim 1, and hence dependent claims 2-13 are in condition for allowance. Prompt notice of allowance is respectfully solicited.

Respectfully submitted,

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AMENDMENTS TO THE CLAIMS

Marked up Version Showing Amendments

Entered as Part of the Current Response

1. (Amended) A method of testing drug sensitivity of cells with respect to a drug, the method comprising the steps of:

(a) preparing a suspension of the cells in a liquid;

(b) exposing a portion of the cells to the drug;

(c) adding at least one substance capable of imparting a measurable degree of fluorescence to the cells in said suspension;

(d) causing the cells to reside individually in defined locations, such that each individual cell corresponds to exactly one of said defined locations, and such that said defined locations [can be individually accessed] are individually accessible by an assay device;

(e) assaying by means of said assay device at least a portion of the cells in said defined locations at least one time [as a means of determining] and correlating a result of an assay conducted by said assay device to the drug sensitivity thereof[.] ;

wherein the drug and said substance capable of imparting a measurable degree of fluorescence are separately applied.